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Description

for Patent Application

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Pertaining to

17-azasteroids substituted at the 21-carbon atom, their use and a method for their manufacture

The invention pertains to new types of 17-azasteroids substituted at the 21-carbon atom, including their salts, their utilization as well as a method for their manufacture.

Subject of the invention are 17-azasteroids substituted at the 21-carbon atom with the general chemical structure of:

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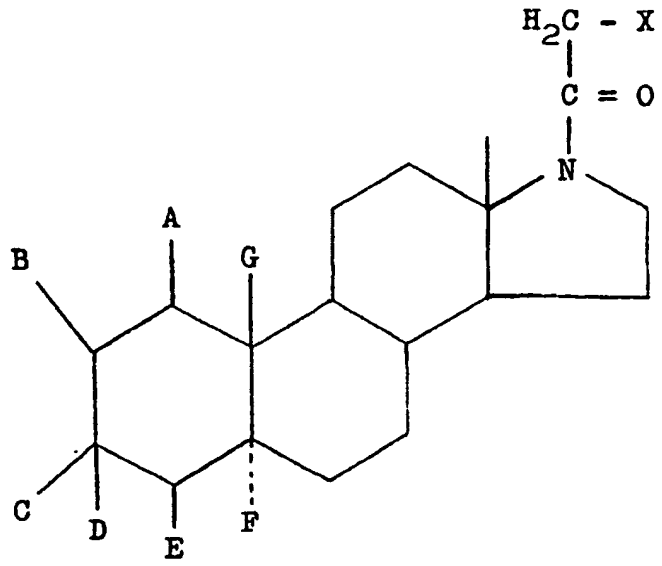


I ,

wherein

A, B, D, B and F represent hydrogen atoms,

C represents a free and, in particular, in the form of ether and ester derivatives masked hydroxy group,

X represents chlorine, bromine, iodine, a hydroxy group, one - possibly substituted - acyloxy group, an alkansulfonyl-oxy group, or a different, largely substituted amino group, and

G represents compounds of the androstane series, represents a methyl moiety, or

AB, DE and **FG** all represent 1 double bond each or

CD represents a free and, in particular, in the form of ketal derivatives masked oxo-group,

as well as its quarternary salts and acid addition salts.

Thus, the invention pertains to such compounds exhibiting at the nitrogen atom, which is located in the 17-position, a pregnane side chain substituted in the 21-position by halogen or a hydroxy, acyloxy, alkansulfonyloxy, or amino group. 17-aza-steroid derivatives are not known from literature.

The invention further pertains to medications containing 1 or more of the above-mentioned compounds as active agent(s) or being composed of these agent(s).

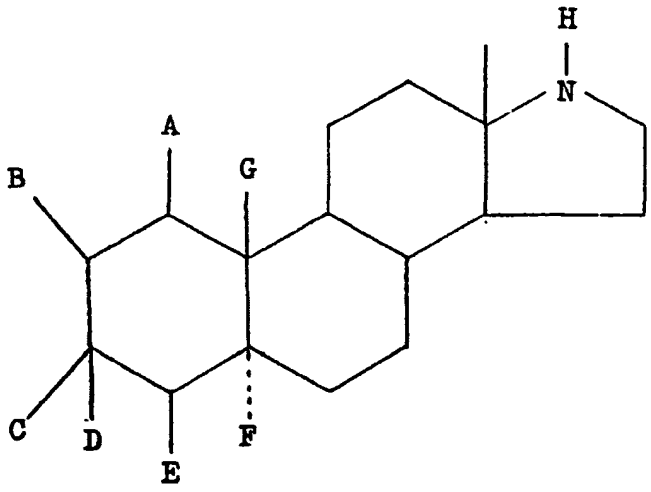
This is because the compounds according to the invention exhibit valuable pharmacological properties. For example, 3,20-dioxo-21-chloro-17-aza-5α-androstane, 3,20-dioxo-21--hydroxy-17-aza-5α-androstane-21-acetate, 3,20-dioxo-21--hydroxy-17-aza-5α-androstane, 3,20-dioxo-21-hydroxy-17--aza-5α-androstane-21-hemisuccinate, 3ß-Hydroxy-20-oxo-21--chlorine-17-aza-5α-androstane, 3ß,21-dihydroxy-20-oxo-17-aza-5α--androstane-21-acetate, and 3ß,21-dihydroxy-20-oxo-17-aza--5α-androstane have a catatoxic effect that stimulates the multi-function oxydase system based on the microsomes of the liver, the value of which is similar to that of spironole acetone. These compounds can also be used for the treatment of icterus gr. neonatorum (acute yellow liver atrophy in newborns), and to influence anomalies caused by excess endogen corticoid production, similar to the effect of 1-[2-chlorophenyl-(1)-4 chlorophenyl]-2,2'-dichlorethane.

21-pyridinium-20-oxo-17-azaestra-1,5,5(10)-trien-3-methyl-ether iodide, 21-triethylammonium-20-oxo-17-azaestra-1,5,5(10)--trien-3-methyletheriodide and some other compounds with a similar structure have a curare-like effect.

21-N-(N'-methylpiperazinyl)-20-oxo-17-azaestra-1,3,5(10)--trien-3-methylether, 5-ethylenedioxy-20-oxo-21-N-(N'-methyl-piperazinyl)-17-aza-5α-androstane and some other compounds with a similar structure have in concentrations of 1 to 5 mg/kg a bacteriostatic effect. In rats, these compounds lower the cholesterol level when administered at a peroral dose of 8 to 14 mg/kg of body weight, preferably at 12 mg/kg of body weight.

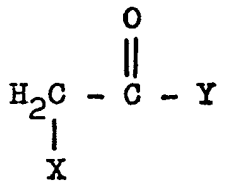
The compounds of the general formula I, whose ring A has aromatic properties, do not exhibit the hormonal effect that is characteristic for estrane derivatives.

An advantageous embodiment of the invention of a method for the manufacture of the formula I compounds described in the invention, which is characterized by the fact that a general chemical structure



II ,

wherein A, B, C, D, E, F and G are configured as indicated, is acylated with a compound of the chemical structure



III ,

via a Schotten-Baumann reaction wherein X and Y represent chlorine and/or iodine, followed by the potentially obtained 17-aza-20-oxo-21-halogensteroid of the general formula I being immediately or after hydrolysis of the potentially in 3-position located ketal group

a) esterified with a carbolic-acid alkali salt, where afterwards - possibly through hydrolysis - the derivative, which potentially exhibits a free hydroxy group at the 21-carbon atom, is produced and as such, if so desired, is transformed into other esters, or

b) brought to reaction with an aliphatic amine with 1 to 6 carbon atoms or with a cyclic amine exhibiting 1 or more hetero-atoms, and the resulting base with the use of acid being potentially transformed into a salt,

is also included.

The compounds according to the invention can preferably be produced individually as follows: a general formula II compound is dissolved or suspended in an aromatic or halogen-containing aliphatic solvent under vigorous agitation, advantageously in benzene or chloroform, and afterwards, an alkali metal hydroxide solution, advantageously sodium hydroxide solution, is added. After cooling to 0 to 5°C and continuing to be agitated vigorously, drops of a general formula III α-halogen carbonic acid halogenide, advantageously chlorine- acetyl-chloride, are added. The mixture is continued to be agitated for several hours and afterwards, the organic phase is separated, washed thoroughly with water, dried and evaporated. The resulting 17-aza-20-oxo-21-halogen steroid derivative can be recrystallized, if necessary.

The general formula I compounds obtained in the manner described above, in which X represents a halogen atom, will be subjected to a substitution reaction, if necessary.

The general formula I 17-aza-steriods substituted in the 31-position by a hydroxy or acyloxy group, can be advantageously produced as follows: 17-aza-2Q-oxo-21-halogensteroid derivatives are dissolved in an aliphatic ketone, preferably acetone. Afterwards, these derivatives are transformed at the boiling point of the solution with alkali salts, preferably potassium salts, by carbonic acids. The ester derivatives generated during the reaction can be transformed by hydrolysis into compounds with free, alcoholic hydroxy groups, and these can again be transformed by carbonic acid anhydrides or carbonic acid halogenides or alkansulfonyl halogenides into other ester derivatives like those with longer carbon chains, for example.

The manufacture of formula I steroid derivates substituted

in the 21-position at a varying degree by amines proceeds advantageously as follows: 17-aza-20-oxo-21-halogen steroid derivatives are dissolved in an inert solvent (like alcohol, ketone, nitrile or ether), preferably ethanol, acetone, acetone nitrile or tetrahydrofurane, and transformed at room temperature or - depending on the type of reaction components - at the boiling temperature of the solvent with amines, e.g. dimethylamine, piperidine, triethylamine, pyridine or N-methylpiperazine. In reactions, where the resulting compound precipitates, the end product is filtered off; in cases, where the end product remains in solution, the solvent if evaporated and the residue is levigated with water, filtered, dried and recrystallized, if necessary. The obtained 20-oxo-17-azasteroids exhibiting the moiety of a secondary or tertiary amine in the 21-position can be transformed into salts in the known manner.

The general formula II compounds used as base materials for the manufacture of the compounds described in this invention with substitutions in the 3-position can be produced from the 16,17-dioxo-16-oximino-5α-androstane or 16,17-dioxo-16-oximino-estra-1,3,5(10)-trien derivatives (US Patent Spec 3 135 772, German Patent Spec 875 650) substituted in the 3-position as follows:

The 16,17-dioxo-16-oximino-5α-androstane or 16,17-dioxo-16-oximinoestra-1,3,5(10)-trien derivatives are dissolved in pure acetic acid at temperatures below the boiling point of this solvent. Afterwards, a mineral acid, preferably sulphuric acid, is added to the homogeneous solution, the reaction mixture is - depending on the temperature sensitivity of the oxim derivate being used - held at a temperature between 20 and 100 °C, followed by the acetic acid solution of the generated

16,17-seco-16,17-dicarbonic acid-5α-androstanimide or 16,17-Seco-16,17-dicarbonic acid estra-1,3,5(10)-trienimide derivatives added to water in the form of drops. The precipitated product is filtered out, washed and dried.

These compounds can also be obtained from 16,17-Seco-16-carbamoyl-17-carbomethoxy-5α-androstane or 16,17-Seco--16-carbamoyl-17-carbomethoxyestra-1,3,5(10)-trien derivatives via a closed ring in an alkaline medium.

The obtained "16,17-seco-16,17-dicarbonic-acidimides" can also be transformed into the corresponding 16-oxo-17-aza-5α-androstane or 16-oxo-17-azaestra-1,3,5(10)-trien derivatives as follows: The compounds are dissolved in a polar solvent, and a methanolic bromine solution or a sodium hypochlorite solution and an alkali metal alcoholate solution, preferably a sodium methylate solution, are added simultaneously. The reactive mixture is agitated first at room temperature and later at the boiling point of the solution. After a reaction period of about 30 minutes the solvent is distilled out, and the residue is levigated with water, filtered out, dried and recrystallized. For the manufacture of these compounds of the lactam type, 16,17-seco-17-carbamoyl-16-carbomethoxy-5α-androstane or 16,17-seco-17--carbamoyl-16-carbomethoxyestra-1,3,5(10)-trien derivatives can also be used as base materials, whereby these substances should preferably be transformed into the 16-oxo-17-aza-5α-androstane or 16-oxo-17-azaestra-1,3,5(10)-trien derivatives in solution in methanol at the boiling temperature with leadtetraacetate, and after removal of the lead salts by alkaline hydrolysis.

The indicated 16,17-seco-16-carbamoyl-17-carbomethoxy derivatives can also be converted into the above-mentioned lactam derivatives through Hoffmann reduction.

In the second stage, the generated 16-oxo-17 aza-5α-androstane or 16-oxo-17-azaestra-1,3,5(10)-trien derivatives are converted by reduction with complex metal hydrides into the general formula II compounds: in doing so, the 16-oxo-17-aza-5α-androstane or 6-oxo-17-azaestra-1,3,5(10)-trien derivatives are advantageously brought to conversion in an ether-type solvent (e.g. tetrahydrofurane or dioxane) or an aromatic solvent (e.g. benzene or toluene)with a benzene solution of lithium aluminum hydride or sodium-to-(2-methoxyethoxy)-aluminum hydride. The reaction mixture is preferably heated for several hours in a nitrogen atmosphere to the boiling temperature; afterwards, the excess reduction agent is reduced in the known manner, the precipitated, gel-type deposit of lithium hydroxide and aluminum hydroxide is filtered out and thoroughly washed, and the filtrate is evaporated. The obtained product is recrystallized or converted into a salt with an inorganic or organic acid, and thus cleaned.

The method of the invention is explained on the following embodiments, which shall not be interpreted as limitations.

Embodiment 1

3-ethylenedioxy-20-oxo-21-chlorine-17-aza-5α-androstane

22.5 g of 3-ethylenedioxy-17-aza-5α-androstane were suspended in 1.350 cm^3 dichloromethane, followed by the addition of 2.200 cm^3 sodium hydroxide solution under vigorous agitation. The suspension was cooled to 0 °C and 80 cm^3 chloroacetyl chloride were added for 90 minutes by pipette. After 30 minutes of agitation at 0 °C the organic phase was separated, and the watery part was extracted 2 times with

300 cm^3 of chloroform each. The combined organic phases were first thoroughly washed with 2 n hydrochloric acid, then with 3% sodium-carbonate solution, and finally with water. After the drying, the solvent was distilled out.

The product was suspended in methanol that had been cooled to 0 °C, filtered and dried. The yield of the 3-ethylenedioxy-20-oxo-21-chlorine-17-aza-5α-androstane obtained with this method was 23.5 g (84% theoretical value); melting point: 212 to 215 °C.

Analysis:

Calculated: C = 66.72%, H = 8.65%, N = 3.53%;
Actual: C = 66.50%, H = 8.78%, N = 3.64%.

Embodiment 2

3,20-dioxo-21-chlorine-17-aza-5α-androstane

10g of 3-ethylenedioxy-20-oxo-21-chlorine-17-aza-5α-androstane were dissolved in 1,000 cm^3 peroxide-free tetrahydrofurane and afterwards, 30 cm^3 of concentrated hydrochloride acid and 30 cm^3 of water were added to the solution. The solution was left standing at room temperature for 24 hours, the pH-value was set to 7, and the tetrahydrofurane was distilled out. Added to the residue were 300 cm^3 water, and the precipitate was filtered out, thoroughly washed with water, and dried. The yield of the 3,20-dioxo-21-chlorine-17-aza-5α-androstane was 8.5 g (86% of theoretical value); melting point: 193 to 195°C (recrystallized from a mixture of benzene and hexane).

Analysis;

Calculated: C = 68.33%, H = 8.60%, N = 3.98%, Cl = 10,07;
Actual: C = 68.15%, H = 8.48%, N = 3.88%, Cl = 9.88%,

Embodiment 3

3,20-dioxo-21-hydroxy-17-aza-5α-androstane--21-acetate

A solution consisting of 2g lithium iodide, 14.3g potassium acetate and 104 cm^3 of water was added to a solution of 5g of 3,20 dioxo-21-chlorine-17-aza-5α-androstane in 900 cm^3 acetone. While adding nitrogen and under vigorous agitation, the reactive mixture was heated 9 hours to the boiling point. Afterwards, about 80% of the solvent were distilled out, the residue was diluted with water, and the precipitate was filtered out and then washed with water and dried. The yield of the obtained 3,20-dioxo-21-hydroxy-17-aza-5α-androstane-21-acetate was 5g (93% of the theoretical value); melting point: 186 to 189°C (recrystallized from watery methanol).

Analysis:

Calculated: C = 70.37%, H = 8.86%, N = 3.73%;
Actual: C = 70.60%, H = 9.05%, N = 3.86%.

Embodiment 4

3,20-dioxo-21-hydroxy-17-aza-5α-androstane

14g of 3,20-dioxo-21-hydroxy-17-aza-5α-androstane-21-acetate were dissolved in 650 cm^3 of methanol, and 30.3 cm^3 of a 21% sodium ethylate solution were added afterwards. The reaction mixture was agitated for 2 hours at room temperature in a nitrogen atmosphere, then the pH-value of the mixture was set to 7, and the methanol was distilled out. The residue was diluted with water, and the precipitate was filtered out, washed with water and dried. The result was 12g (96% of the

theoretical value) of 3,20-dioxo-21-hydroxy-17-aza-5α-androstane; melting point: 210 to 211°C (recrystallized from isopropanol).

Analysis:

Calculated: C = 72.03%, H = 9.37%, N = 4.20%;
Actual: C = 71.87%, H = 9.36%, N = 4.25%.

Embodiment 5

3,20-dioxo-21-hydroxy-17-aza-5α-androstane- 21-hemisuccinate

5 grams of 3,20 dioxo-21-hydroxy-17-aza-5α-androstane were dissolved in 80 cm^3 of anhydrous pyridine, followed by the addition of 5 grams of succinic acid hydride. The reaction mixture was left standing for 48 hours at room temperature, and then poured into ice water. The pH-value of the solution was set to 2.5 to 3.9, and the precipitate was filtered out, washed with water and dried. The result was 6 grams (93% of the theoretical value) of 3,20-dioxo-21-hydroxy-17-aza-5α-androstane-21-hemisuccinate; melting point: 222 to 223°C (boiled in acetone).

Analysis:

Calculated: C = 66.49%, H = 8.19%, N = 3.23%;
Actual: C = 66.53%, H = 8.27%, N = 3.35%.

Embodiment 6

Sodium salt of 3,20-dioxo-21-hydroxy-17-aza-5α-androstane-21-hemisuccinate

A solution of 0.197 grams of sodium carbonate and 30 cm^3 of water was added to a solution of 1.04 grams of 3,20-dioxo-21-hydroxy-17-aza-5α-androstane-21-hemisuccinate in 60 cm^3 of

ethanol under vigorous agitation. Thereafter, the solution was dry-evaporated under vacuum at temperatures below 30 °C. The product was washed with anhydrous ethanol and ether. The result was 1 gram (91% of the theoretical value) of the sodium salt of 3,20-dioxo-21-hydroxy-17-aza-5α-androstane-21-hemisuccinate.

Analysis:

Calculated: C = 63.27%, H = 7.52%,
Actual: C = 65.12%, H = 7.59%.

Embodiment 7

3ß-Hydroxy-20-oxo-21-chlorine-17-aza-5α-androstane

3 grams of 3ß-hydroxy-17-aza-5α-androstane were processed as in Embodiment 1. The result was 3 grams (79% of the theoretical value) of 3ß-hydroxy-20-oxo-21-chlorine-17-aza-5α-androstane; melting point: 220 to 222°C.

Analysis:

Calculated: C = 67.87%, H = 9.11%, N = 3.96%, Cl = 10.00%;
Actual: C = 67.75%, H = 9.20%, N = 4.05%, Cl = 9.85%.

Embodiment 8

3ß,21-dihydroxy-20-oxo-17-aza-5α-androstane--21-acetate

6.5 grams of 3ß-hydroxy-20-oxo-21-chlorine-17-aza-5α-androstane were processed as described in Embodiment 3. The yield was 6 grams (93% theoretical) 3ß,21-dihydroxy-

-20-oxo-17-aza-5α-androstane-21-acetate; melting point; 183 to 184 °C (recrystallized from a mixture of isopropanol and hexane).

Analysis:

Calculated: C = 69.99%, H = 9.35%, N = 3,71%;
Actual: C = 69.80%, H = 9.40%, N = 3.80%.

Embodiment 9

3ß,21-dihydroxy-20-oxo-17-aza-5α-androstane

3.7 grams of 3ß,21-dihydroxy-20-oxo-17-aza-5α-androstane-21-acetate were processed as described in Embodiment 4. The yield was 3 grams of 3ß,21-dihydroxy-20-oxo-17--aza-5α-androstane (91% theory); melting point: 227 to 229°C (recrystallized from methanol).

Analysis:

Calculated: C = 71.60%, H = 9.92%, N = 4.18%;
Actual: C = 71.42%, H = 9.99%, N = 4.25%.

Embodiment 10

3,20-dioxo-21-hydroxy-17-aza-5α-androstane-
-21-methanesulfonate

1 gram of 3,20-dioxo-21-hydroxy-17-aza-5α-androstane was dissolved in 70 cm^3 pyridine, and the solution was cooled to 0°C. Afterwards, 2.6 cm3 methane sulfonic acid chloride were added to the agitated solution for about 15 minutes. The mixture was agitated for 3 hours at 0°C and subsequently, drops of water were added at 2 to 5°C. The precipitate was filtered out, washed with

5% hydrochloric acid and then with water, and dried. The result was 1 gram (81% of theory) of 3,20-dioxo-21-hydroxy-17-aza-5α-androstane-21-methanesulfonate; melting point: 146 to 148°C (recrystallized from methanol).

Analysis:

Calculated: C = 61.36%, H = 8.09%, N =5.41%, S = 7.80%
Actual: C = 61.25%, H = 8.18%, N = 5.46%, S = 7.71%.

Embodiment 11

21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien--3-methylether

9.3 grams of 17-azaestra-1,3,5(10)-trien-3-methyl-ether were processed as described in Embodiment 1. The result was 9.3 grams (78% of theory) of 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether; melting point: 197 to 198°C.

Analysis:

Calculated: C = 69.05%, H = 7.53%, N = 4.03%;
Actual: C = 69.15%, H = 7.40%, N = 4.12%.

Embodiment 12

21-pyridinium-20-oxo-17-azaestra-1,3,5(10)--trien-3-methyletheriodide

Added to a solution of 1 gram of 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether in 280 cm3 acetone were 1.3 grams of lithiumiodide und 1.7 cm3 of pyridine. The mixture was heated for 4 hours with the introduction of nitrogen and under reflux to boiling. The precipitated 21-pyridinium-20-oxo-17-azaestra-1,3,5(10)-

trien-3-methyletheriodide was filtered out, washed with acetone and dried. The yield was 1.2 grams (91% of theory); melting point; 239 to 240°C

Analysis:

Calculated: C = 57.93%, H = 6.02%, N = 5.40%, I = 24.49%;
Actual: C = 57.80%, H = 6.12%, N = 5.35%, I = 24.59%.

Embodiment 13

21-triethylammonium-20-oxo-17-azaestra-1,3,5(10)--trien-3-methyletheriodide

Added to a solution of 1 gram of 21 chlorine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether in 280 cm^3 acetone were 1.3 grams of lithiumiodide and 2.5 cm^3 triethylamine. The mixture was subsequently heated to the boiling point for 4 hours in a nitrogen atmosphere. The precipitate was filtered out, washed with acetone and dried. The result was 1.3 grams (86% of theory) of 21-triethylammonium-20-oxo-17-azaestra-1,3,5(10)-trien-3-methyletheriodide; melting point: 214 to 216°C (recrystallized from methanol).

Analysis:

Calculated: C = 57.77%, H = 7.65%, N = 5.18%, I = 23.47%;
Actual: C = 57.77%, H = 7.80%, N = 5.23%, I = 23.47%.

Embodiment 14

21-iodine-20-oxo-17-azaestra-1,3,5(10)-trien--3-methylether

Added to a solution of 3 grams of 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether in 600 cm^3 acetone

were 4 grams of sodium iodide. The mixture was heated to the boiling point for 30 minutes in a nitrogen atmosphere. The precipitated sodium chloride was filtered out, the filtrate was evaporated under vacuum, the residue was suspended in water, and the released 21-iodine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether was filtered out and dried. The yield was 3.7 grams (97.5% of theory); melting point: 180 to 182°C.

Analysis:

Calculated: C = 54.68%, H = 5.89%, N = 3.15%, I = 28.55%;
Actual: C = 54.50%, H = 5.99%, N = 3.23%, I = 28.62%.

Embodiment 15

21-hydroxy-20-oxo-17-azaestra-1,3,5(10)-
-trien-3-methylether-21-acetate

7.7 grams of 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-
-trien-3-methylether were processed as described in Embodiment 3. The yield was 8 grams (94% of theory) of 21-hydroxy-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether-21-acetate; melting point: 172 to 174°C (recrystallized from methanol).

Analysis:

Calculated: C = 71.14%, H =7,87%, N = 3,77%;
Actual: C = 71,18%, H =7,95%, N = 3,85%.

Embodiment 16

21-N-(N'-methylpiperazinyl)-20-oxo-17-azaestra-
-1,3,5(10)-trien-3-methylether

1 gram of 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether was dissolved in 7.6 cm^3 benzene and 88 cm^3 acetonitrile with 0.3 grams of N-methylpiperazine and 0.015 grams of sodium iodide added thereafter. The mixture - under introduction of nitrogen - was then kept at 60 °C for 4 hours. Afterwards, the solvent was distilled out, the residue was levigated with water, and the precipitate was washed with water and dried. The obtained steroid base (melting point: 155 to 157 °C) was dissolved in ethanol, and thereafter the 21-N-(N'-methylpiperazinyl)-20-oxo-17-azaestra-1,3,5(10)-trien-3-methyletherdihydrochloride was separated with hydrochloric ethanol. The product was recrystallized from a mixture of methanol and acetone. The yield was 1.3 grams (98% of theory); melting point: 170 to 172°C.

Analysis:

Calculated: C = 72.93%, H = 9.06%, N = 10.21%;
Actual: C = 73.00%, H = 9.00%, N = 10.25%.

Embodiment 17

3-ethylenedioxy-20-oxo-21-N-(N'-methylpiperazinyl)-
-17-aza-5α-androstane

0.88 grams of 3-ethylenedioxy-20-oxo-21-chlorine-17-aza-5α-androstane were processed as described in Embodiment 16. The yield was 1 gram of 3-ethylenedioxy-20-oxo-21-N-(H'-methylpiperazinyl)-17-aza-5α-androstane-dihydrochloride (97% of theory); melting point: 242 to 244°C (recrystallized from methanol).

Analysis:

Calculated: C = 70.56%, H = 9.86%, N = 9.14%;
Actual: C = 70.4-0%, H = 9.86%, N = 9.25%.

Embodiment 18

21-N-(N'-methylpiperazinyl)-20-oxo-17--azaestra-1,3,5('10)-trien-3-methylether

2 grams of 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien--3-methylether were dissolved in a mixture of 150 cm^3 benzene and 170 cm^3 acetonitrile, and 6 grams of N-methylpiperazine were added thereafter. The reaction mixture was held for 6.5 hours at 70 °C followed by the solvent being distilled out and the residue being levigated with water. The precipitate was filtered out, thoroughly washed with water, and dried. The obtained steroid base (melting point: 155 to 157°C) was dissolved in ethanol, and the 21-N-(N'-methylpiperazinyl)-20-oxo-17-azaestra-1,3,5(10)-trien-3-methyletherdihydrochloride was separated with hydrochloric ethanol. The product was recrystallized from a mixture of methanol and acetone. The yield was 2.2 grams (78% of the theory); melting point: 169 to 171°C.

Analysis:

Calculated: C = 72.93%, H = 9.06%, N = 10.21%;
Actual: C = 72.58%, H = 8.91%, N = 10.00%.

Patent Claims

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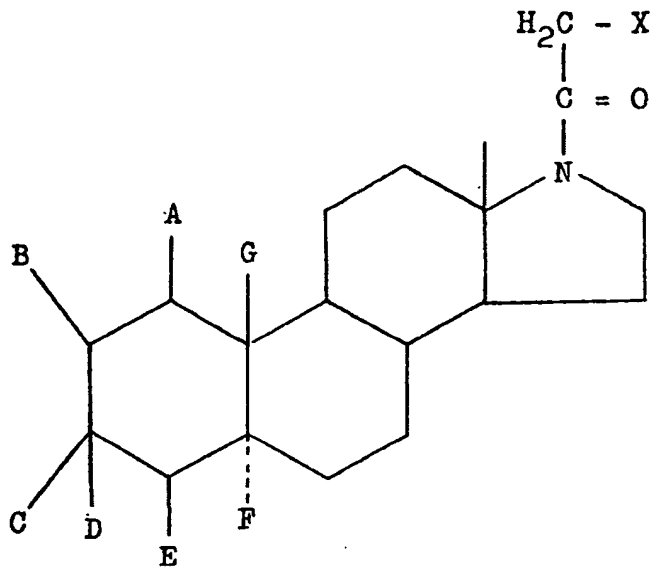
Patent Claims

6 17-azasteroids substituted at the 21-carbon atom of the general chemical formula



I ,

wherein

A, B, D, E and P represent hydrogen atoms,

C represents a free or, in particular special hydroxy group masked in the form of ether or ester derivatives,

X represents chlorine, bromine, iodine, a hydroxy group, a - possibly substituted - acyloxy group, an alkansulfonyl-oxy group, or a different, largely substituted amino group, and

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G	in the case of androstane compounds) represents a methyl moiety or
AB, DE and FG	all represent 1 double bond each or
CD	represents a free oxo group, in particular, masked in the form of the ketal derivative,

as well as its quarternary salts and acid addition salts.

2.) 17-azasteroids according to claim 1, wherein the acyloxy group, which may be represented by X, exhibits 1 to 6, in particular, 1 or 2 carbon atoms.

3.) 17-azasteroids according to claim 1 or 2, wherein the acyloxy group, which may be represented by X, is substituted by a carboxyl group.

4.) 17-azasteroids according to claim 1 to 3, wherein the acyloxy group, which may be represented by X, is the acetyl group or the hemisuccinyl group.

5.) 17-azasteroids according to claim 1 or 2, wherein the alkansulfonyloxy group, which may be represented by X, is the methanesulfonyloxy group.

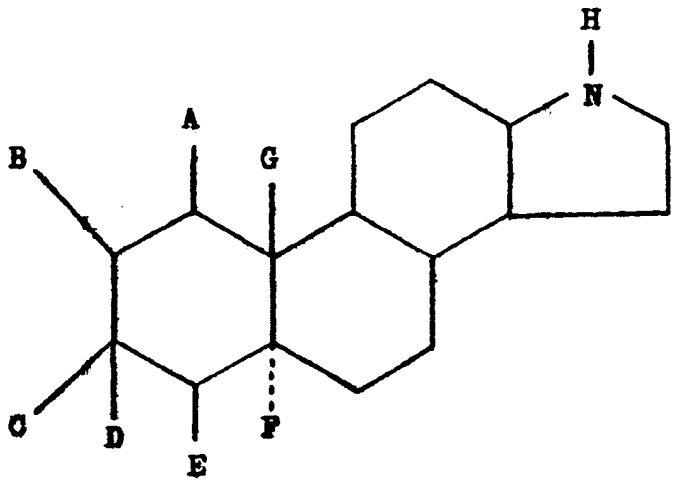
6.) 17-azasteroids according to claim 1, wherein the substituted amino group, which may be represented by X, is an alkyl-substituted amino group, preferably a group, whose alkyl-moiety or alkyl-moieties each exhibit 1 to 6, in particular, 1 to 4 carbon atom(s).

7.) 17-azasteroids according to claim 1, wherein the substituted amino group, which may be represented by X, is a group, whose nitrogen is part of hetero-cyclic ring, which may exhibit 1 or more additional hetero-atoms.

8.) 17-azasteroids according to claim 1 or 7, wherein the hetero-cyclic ring, which may be represented by X, is a pyridine ring, a piperidine ring, or an alkyl-substituted, preferably methyl-substituted piperazine ring is, which may extend from a nitrogen atom different from the nitrogen atom extending from the 21-carbon atom.

9.) Pharmaceutical, characterized by a content of 1 or more compounds according to claim 1 to 8 as its active agent or agents.

10.) Method for the manufacture of the compounds according to claim 1 to 8, wherein a compound of the general formula



II ,

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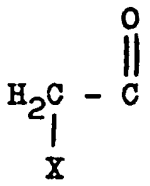
wherein A, B, C, D, E, F and G are defined as indicated in claims 1 to 8 is acylated with a compound with the general chemical formula



III ,

wherein X and Y represent chlorine and/or bromine and/or iodine, via a Schotten-Baumann reaction, wherein X and Y represent chlorine and/or iodine, followed by the potentially obtained 17-aza-20-oxo-21-halogensteroid of the general formula I immediately or after hydrolysis of the potentially in 3-position located ketal group being

a) esterified with a carbolic-acid alkali salt, where afterwards - possibly through hydrolysis - the derivative, which potentially exhibits a free hydroxy group at the 21-carbon atom, is produced and as such, if so desired, is transformed into other esters, or

b) is brought to reaction with an aliphatic amine with 1 to 6 carbon atoms or with a cyclic amine exhibiting 1 or more hetero-atoms, and the resulting base with the use of acid being potentially transformed into a salt.

11.) Method according to claim 10, wherein an α-halogen-carbonic acid-halogenide, preferably, chlorineacetylchloride, is used for the acylation.

12.) Method according to claim 10 or 11, wherein the acylation is performed in an aromatic or halogen-containing, aliphatic solvent, preferably in benzene or

dichloromethane, and in the presence of an alkali metal, preferably sodium hydroxide.

13.) Method according to claim 10a, wherein the esterification is performed in an aliphatic ketone, preferably acetone, at the boiling point of the solvent.

14.) Method according to claim 10b, wherein the amination is performed in an inert solvent, preferably in ethanol, acetone, acetonitrile or tetrahydrofurane.

15.) Method according to claim 10, 13 or 14, wherein the esterification or amination of the general formula I 12-aza-20-keto-21-halogensteroids is performed in the presence of sodium or lithium iodide, preferably under introduction of nitrogen.

16.) Method according to claim 10 to 12, wherein 3-ethylenedioxy-17-aza-5α-androstane is acylated with chlorineacetylchloride into 3-ethylenedioxy-20-oxo-21-chlorine-17-aza-5α-androstane.

17.) Method according to claim 10, wherein 3-ethylenedioxy-20-oxo-21-chlorine-17-aza-5α-androstane is hydrolized with a watery hydrochloric acid solution into 3,20-dioxo-21-chlorine-17-aza-5α-androstane.

18.) Method according to claim 10a, 13 or 15,wherein 3,20-dioxo-21-chlorine-17-aza-5α-androstane is esterified with potassium acetate into 3,20-dioxo-21--hydroxy-17-aza-5α-androstane-21-acetate.

19.) Method according to claim 10a, wherein 3,20-dioxo-21-hydroxy-17-aza-5α-androstane-21-acetate is hydrolized in an alkaline medium into 3,20-dioxo-21-hydroxy-17-aza-5α-androstane.

20.) Method according to claim 10a, wherein 3,20-dioxo-21-hydroxy-17-aza-5α-androstane is esterified with succinic acid hydride into 3,20-dioxo-21-hydroxy-17--aza-5α-androstane-21-hemisuccinate.

21.) Method according to claim 10 to 12, wherein 3ß-hydroxy-17-aza-5α-androstane is acylated with chlorine-acetylchloride into 3ß-hydroxy-20-oxo-21-chlorine-17-aza-5α-androstane.

22.) Method according to claim 10a, 13 or 15, wherein 3ß-hydroxy-20-oxo-21-chlorine-17-aza-5α-androstane is esterified with potassium acetate into 3ß-21-dihydroxy-20-oxo-17-aza-5α-androstane-21-acetate.

23.) Method according to claim 10a, wherein 3ß,21-dihydroxy-20-oxo-17-aza-5α-androstane-21-acetate is hydrolized in an alkaline medium into 3ß,21-dihydroxy--20-oxo-17-aza-5α-androstane.

24.) Method according to claim 10 to 12, wherein 17-azaestra-1,3,5(10)-trien-3-methylether is acylated with chlorineacetylchloride into 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether.

25.) Method according to claim 10b, 14 or 15, wherein 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether is converted with pyridine in the presence of lithium iodide into 21-pyridinium-20-oxo-17--azaestra-1,3,5(10)-trien-3-methyletheriodide.

26.) Method according to claim 10b, 14 or 15, wherein 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether is converted with triethylamine in the presence of lithium iodide into 21-triethylammonium-20-oxo-17-azaestra-1,3,5(10)-trien-3-methyletheriodide.

27.) Method according to claim 10a, 13 or 15, wherein 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether is esterified with potassium acetate into 21-hydroxy-20-oxo-17-azaestra-1,3,5(10)-trien-3--methylether-21-acetate.

28.) Method according to claim 10b, 14 or 15, wherein 21-chlorine-20-oxo-17-azaestra-1,3,5(10)-trien-3-methylether is converted with N-methylpiperazine into 21-N-(N'-methylpiperazinyl)-20-oxo-17-azaestra--1,3,5(10)-trien-3-methylether.

29.) Method according to claim 10b, 14 or 15, wherein 3 ethylenedioxy-20 oxo-21-chlorine-17-aza-5α-androstane is converted with N-methylpiperazine into 3-ethylene-dioxy-20-oxo-21-N-(N'-methylpiperazinyl)-17-aza-5α--androstane.

30.) Method for the manufacture of compounds according to claim 1, for which X represents iodine, wherein compounds according to claim 1, for which X represents chlorine or bromine, are converted with alkali-iodides, preferably, sodium iodide.

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